IN an unusual step, the US National Eye Institute has announced it will fund a large-scale clinical trial that could dramatically lower the cost of anti-VEGF therapy that can improve vision for patients with wet age-related macular degeneration (AMD). The trial will compare the safety and efficacy of intravitreal injections of the anti-cancer drug bevacizumab (Avastin, Genentech) head-to-head with ranibizumab (Lucentis, Genentech) for treating AMD.

Both compounds have been shown to improve vision in significant numbers of wet AMD patients. They work by blocking the action of vascular endothelial growth factor, or VEGF, an enzyme that promotes new blood vessel growth and mediates vessel wall permeability. Blocking the enzyme is thought to impede development of and leakage from abnormal subfoveal choroidal blood vessels, which are responsible for vision loss in AMD.

“Until about a year ago we would give wet AMD patients a hug and say ‘good luck,’ because there really wasn’t much we could do for them. Now we can save or improve their vision in 85 per cent of cases,” said William Rich III, MD, FACS, medical director of health policy for the American Academy of Ophthalmology in Las Vegas.

If successful, the NEI-sponsored trial would resolve the conflict. Its most likely would result in widespread regulatory approval of bevacizumab for AMD use, making anti-VEGF treatment affordable worldwide, and encouraging doctors to use it.

“It is a quality-of-care issue first and an economic issue second. This will have a huge impact on our ability to treat AMD patients. We have the opportunity to save the vision of hundreds of thousands of people worldwide without the resources to pay for current therapies approved by the Food and Drug Administration,” Dr Rich said.

Why a government-funded trial?

While the US NEI has spent about €71m supporting more than 300 studies examining how VEGF influences eye diseases, it typically limits its role to funding basic research and small clinical studies. The large-scale randomised clinical trials required to support regulatory approval are usually underwritten by pharmaceutical companies.

But neither US-based Genentech, which developed and manufactures both ranibizumab and bevacizumab, nor Switzerland-based Roche, which distributes bevacizumab outside the US, has any interest in testing bevacizumab for ocular use. Genentech and Roche spokespersons both told EuroTimes they are instead focusing on expanding indications for bevacizumab as a cancer treatment, including lung cancer and breast cancer. Genentech and Novartis, which distribute Lucentis outside the US, are focusing on expanding indications for ranibizumab for ocular diseases, including diabetic macular oedema and retinal vein occlusion.

“Our mission is to meet unmet medical need,” explained Dawn Kalmar, senior manager of corporate relations for Genentech. It took 10 years of clinical research and millions of dollars to develop ranibizumab for ocular use, she noted. Absent the prospect of greatly improved clinical performance, duplicating that effort to establish safety, dosing and clinical indications for ocular use of bevacizumab would be inconsistent with Genentech’s mission and a waste of resources, she said.

“We don’t think that is in the best interest of patients when we can make Lucentis available to them.”

Needless to say, Genentech also has a huge financial interest in maintaining the Lucentis franchise. Approved for sale in the US on June 30, 2006, US Lucentis sales jumped from €7.6m in the second quarter to €116m in the third quarter. Lucentis sales are expected to be a significant driver of Genentech’s revenue growth for the next few years, according to analyst Andrew Fellows at the Swiss brokerage Helvea.

By comparison, US Avastin sales totalled €337m in the third quarter of 2006, up 34 per cent from the same period in 2005. While widespread ocular use of bevacizumab would further increase Avastin sales, to the extent that those increases reduced Lucentis sales, they could represent a net loss for Genentech.

Without industry support, the project falls to government. The project is a good fit for the US National Institutes of Health, which has made angiogenesis a major focus for decades, investing more than €430m in more than 1,900 studies.

“Avastin is a drug that has helped patients. We do not want any patients to be left behind,” said Paul A Sieving, MD, PhD, director of the NEI.

System costs drive government decision

Of course, cost – particularly that paid directly by patients – is the biggest threat to Lucentis use. In the US, about 16 per cent of the population has no insurance at all, leaving patients liable for the entire cost of all care. Even many who are insured face large out-of-pocket expenses in the form of co-payments (a fixed fee assessed for each service or drug received), typically ranging from €7.50 to €30 for an injectable, or a prescription refill), deductibles (a requirement that patients pay a set amount of healthcare costs before insurance kicks in, typically ranging from €190 to as much as €37,775 per person annually) and co-insurance (a requirement that patients pay a percentage of all charges incurred, often 10 per cent to 20 per cent).

For example, patients covered by Medicare without supplemental private drug insurance would be responsible for 20 per cent of the cost of Lucentis, or about €6,000 for a two-year course. About 22 per cent of Medicare patients lack such supplemental coverage, Dr Rich said.

Genentech emphasises its commitment to patient access. W hile Kalmar said that the vast majority of Lucentis patients spend less than €38 out-of-pocket per dose, the firm operates a programme that assists lower-income patients faced with large out-of-pocket expenses. The programme also benefit the pharmaceutical industry, Dr Rich noted. By donating the drugs to a third party for distribution, the industry avoids discounting prices. This increases payments from Medicare and other insurers that link reimbursement for drugs to the average price paid for the drug on the open market.

Dr Rich allows that the benefits of assistance programmes offered by Genentech and other pharmaceutical manufacturers are generous, typically providing assistance to individuals with incomes up to 300 per cent of the officially recognised US poverty level, or about €38,000 for a family of three. But on the ground, such programmes are cumbersome. Patients often are unwilling or unable to provide the information required to qualify for assistance. They also require additional paperwork from the physician, driving up overhead costs.

As a result, even in the US, many physicians, such as Randy Johnson, MD, a retina specialist practising in Cheyenne, Wyoming, continue to offer patients a choice of bevacizumab or ranibizumab. He began treating advanced AMD patients with bevacizumab in March 2006, about four months before ranibizumab was available, and still uses bevacizumab about three times as often as ranibizumab.

Currently, Medicare payment rules allow...
reimbursement for either treatment for AMD.

However, not all ophthalmologists are willing to experiment with an off-label medication, even to save significant money. That bevacizumab has not undergone a large-scale clinical trial raises legitimate concerns about safety and long-term efficacy – and liability in case of a poor outcome or complication.

But as much as drug companies focus on patient out-of-pocket costs, insurance costs also matter, even in America. And the very high cost of ranibizumab has not gone unnoticed by Medicare. Indeed, an independent Medicare advisory panel found the growing body of evidence that bevacizumab may be just as effective as ranibizumab at a far lower price compelling. Their recommendation that the NEI fund a head-to-head study carried great weight, Dr Rich said. The AAO board added its endorsement in a letter to the NEI. “The feeling of the academy’s board of trustees was the need to document to the world the efficacy and safety of Avastin for ocular use,” Dr Rich said.

Of course, ophthalmologists also have a stake in how much money Medicare spends on drugs, at least indirectly. Because overall Medicare budgets are fixed; any extra drug costs reduce funds available for physician payments. While the cost impact of adding any single new drug or treatment is minor because it is diluted across the entire universe of physicians, the cumulative impact of skyrocketing technology costs puts extreme pressure on physician payments. Doctors must fight every year to avoid proposed Medicare payment cuts of as much as seven per cent. A growing realisation of this connection is mobilising many US doctors to support a much more critical approach to the cost-effectiveness of new treatments.

**Trial could be challenged**

At press time, details of the NEI trial were not set. Daniel Martin, MD, of Emory University in Atlanta, US is the lead investigator. But neither his office nor the NEI would release any information on the protocol, how many patients will be enrolled, the timeframe or budget for the study.

Dr Rich is optimistic that enrolment will begin within a few months. However, he believes there could be attempts to interfere with the trial.

“The device and drug industry doesn’t like to see head-to-head trials, particularly ones that could have this much economic impact,” Dr Rich said. He speculated that the impact could reach €4bn or more.

But Dr Rich said he didn’t expect Genentech to interfere. “It is a highly ethical firm."

Others, though, might challenge the trial on the basis that Medicare will pay for the drugs used in the trial, but not for the trial itself. Under current Medicare guidelines for funding experimental treatments, the trial appears to qualify, he said. But if a challenge were to succeed it would be a setback.

He believes, though, that any attempt to stop the trial would backfire. “It would be a public relations nightmare to interfere in a trial that would have such enormous economic and health benefits. The evidence is overwhelming that even saving a little bit of vision has enormous impact on the quality of life. It is the right thing to do.”

— William Rich III, MD, FACS